IN THE SPECIFICATION:

Please insert after page 26, but before the claims, the attached paper Substitute Sequence Listing in the specification.

Attachments: Substitute Sequence Listing (paper copy)
Substitute Sequence Listing (computer readable copy, (CD-R)).

Please amend page 2, line 20-page 4 line 10 as follows:

As a result, BCR-ABL has become a target for the development of therapeutics to treat leukemia. Most recently, ~~Gleevec®~~ GLEEVEC® (STI571), a small molecule inhibitor of the ABL kinase, has been approved for the treatment of CML. This drug is the first of a new class of anti-proliferative agents designed to interfere with the signaling pathways that drive the growth of tumor cells. The development of this drug represents a significant advance over the conventional therapies for CML and ALL, chemotherapy and radiation, which are plagued by well known side-effects and are often of limited effect since they fail to specifically target the underlying causes of the malignancies. However, Gleevec®, like many other therapeutics in development, only targets a single signaling protein among several implicated in the progression of the disease.

Clinical results since the introduction of ~~Gleevec®~~ GLEEVEC® have shown that patients often develop resistance to ~~Gleevec®~~ GLEEVEC®. *See, e.g. Sawyers, Science* 294(5548): 1834 (2001). The mechanism of resistance may vary from patient to patient, but is most often a result of mutations in the BCR-ABL DNA that results in a variant kinase that is not affected by the inhibitor. See, e.g., Mercedes, Science 294(5548): 1834 (2001). Resistance may also occur through increased expression of the BCR-ABL protein. *See, e.g. Keeshan, Leukemia* (12):1823-33 (2001). Improved BCR-ABL kinase inhibitors are now being developed that will target the mutant forms of BCR-ABL kinase. Patients may be switched to these inhibitors, or to increased doses of ~~Gleevec®~~ GLEEVEC®, depending upon the ability to detect restored BCR-ABL expression in patient samples. Accordingly, in order to most effectively treat CML patients, it will be crucial to develop a suitable assay for detecting BCR-ABL expression and kinase activity in patients undergoing ~~Gleevec®~~ GLEEVEC® treatment.

Presently, tumor burden or residual disease and BCR-ABL expression in CML patients is detected by genetic tests such as FISH. This test has the drawbacks of being unreliable for some labs and being expensive. In addition, the mRNA level in a sample may not correlate with the protein level or activity of BCR-ABL. Accordingly, the development of a simpler, less costly, antibody-based test for detecting BCR-ABL activity would be desirable. The BCR-ABL fusion protein may presently be detected by using antibodies against either the wild type BCR (SEQ ID NO:2) or c-ABL proteins (SEQ ID NO:3). *See, e.g., Wang and Arlinghaus, Cancer Research* 51(11): 3048-51 (1991); U.S. Patent No. 5,369,008 (Issued November 29, 1994). This approach does not employ a single BCR-ABL fusion protein specific antibody. Similar approaches have been described employing multiple antibodies, each specific for a different epitope in either wild-type BCR and ABL, in an attempt to detect BCR-ABL fusion protein. *See Berendes et al.*, U.S. Patent No. 6,610,498 (Issued August 26, 2003). Again, this approach does not employ a single antibody that is truly BCR-ABL fusion protein-specific, as the antibodies do not bind a unique epitope present only in the BCR-ABL fusion junction region. These methods are further limited by time-consuming biochemical techniques, such as Western blots, that must be employed to separate the signal of the BCR-ABL fusion protein itself from the signal of the wild type protein. Accordingly, the current reagents and methods are not well suited for clinical use.

Please amend page 4, line 29-page 5 line 8 as follows:

Presently, CML cells are identified using flow cytometry through the use of a number of cell-surface markers, but this assay is not precise and may result in misidentifying normal cells as CML cells. Development of new antibodies that specifically detect the BCR-ABL fusion protein would enable more direct and reliable identification of CML cells, and would be well suited to the clinical analysis of BCR-ABL kinase activity using sensitive and widely-used techniques such as immuno-histochemistry (IHC) and flow cytometry (FC). Such new methods would greatly assist in optimally treating each CML patient as resistance to ~~Gleevec®~~ GLEEVEC® or other BCR-ABL targeted therapies develops.

Please amend page 5, lines 10-19 as follows:

The invention provides novel antibodies that specifically detect the human P210 BCR-ABL fusion protein, which results from the Philadelphia chromosome translocation involving wild-type BCR (SEQ ID NO:2) and c-ABL (SEQ ID NO:3). Also provided are methods for determining the protein expression level or activity of BCR-ABL in a biological sample, profiling BCR-ABL protein expression in a test tissue, and identifying a compound that modulates BCR-ABL expression or activity, by using a BCR-ABL fusion protein specific antibody. In some embodiments, the sample or test tissue is taken from a subject having or suspected of having a disease, such as CML, in which the BCR-ABL genetic translocation is implicated.

Please amend page 9, line 26-page 8 line 7 as follows:

Further provided by the present invention are novel and powerful new methods of using a BCR-ABL specific antibody to identify patient samples that contain disease cells implicating the BCR-ABL translocation, for example, CML patients. Detection of BCR-ABL in a biological sample may be carried out in a variety of clinically-suitable assay formats, such as flow cytometry or by immunocytochemistry. Antibodies of the invention also enable new methods for the quantitative analysis of BCR-ABL expression levels, which may be translated into a measurement of tumor burden or drug effectiveness, for example, effectiveness of ~~Gleevec®~~ GLEEVEC® therapy in a CML patient.

Please amend page 13, lines 4-15 as follows:

The invention also provides immortalized cell lines, such as hybridoma clones, constructed as described above, that produce BCR-ABL monoclonal antibodies of the invention. Similarly, the invention includes recombinant cells producing a BCR-ABL antibody as disclosed herein, which cells may be constructed by well known techniques; for example the antigen combining site of the monoclonal antibody can be cloned by PCR and single-chain antibodies produced as phage-displayed recombinant antibodies or soluble antibodies in E. coli (*see, e.g.*, ANTIBODY ENGINEERING PROTOCOLS, 1995, Humana Press, Sudhir Paul editor.) Hybridomas and BCR-ABL fusion junction specific antibodies provided by the invention include

hybridoma clone #4H3, deposited on 15 March 9, 2004, ATCC Accession No. PTA-5851, at ATCC P.O.Box 1549 Manassas, VA 20108 USA.

Please amend page 16, line 13-page 17 line 6 as follows:

In certain preferred embodiments, the biological sample has been contacted with at least one BCR-ABL inhibitor or is obtained from a subject treated with such inhibitor. Accordingly, changes in BCR-ABL expression resulting from contacting a biological sample with a test compound, such as a BCR-ABL inhibitor, may be examined to determine effect of such compound. Exemplary inhibitors of BCR-ABL include, but are not limited to of ~~Gleevec®~~ GLEEVEC® (STI-571), and its analogues. Inhibitory compounds may be targeted inhibitors that modulate post-kinase activity of BCR-ABL, or may be upstream expression inhibitors, such as siRNA or anti-sense inhibitors. In another preferred embodiment, the compound is being tested for inhibition of BCR-ABL activity or expression. Such compound may, for example, directly inhibit BCR-ABL activity, or may indirectly inhibit its activity by, *e.g.,* inhibiting another kinase that phosphorylates and thus activates BCR-ABL.

Biological samples may be obtained from a subject at risk of, potentially, or suspected of, having a disease or condition involving altered BCR-ABL expression or activity (*e.g.,* CML, ALL). For example, samples may be analyzed to monitor subjects who have been previously diagnosed as having CML, to screen subjects who have not been previously diagnosed as having CML, or to monitor the desirability or efficacy of therapeutics targeted at BCR-ABL. In the case of CML, for example, the subjects will most frequently be adult patients undergoing ~~Gleevec®~~ GLEEVEC® treatment and are at risk for the development of ~~Gleevec®~~ GLEEVEC® resistance.